REMARKS

I. Status of Claims

Upon entry of the present amendment to the claims, claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-60 will be pending and under examination in this application, claims 1-20, 23, 25, 26, 28, 29, 32, 33, 37, 38, 40, 41, 44, and 45 having been previously cancelled and claims 53-60 newly added. Support for the new claims can be found throughout the specification, e.g., at page 8, lines 18-25; page 10, lines 5-7 and 29-32; and Example 1 at page 13, lines 12-24 of the substitute application filed on September 28, 2006. No new matter is added.

II. Rejections Under 35 U.S.C. § 103(a)

Claims 21, 22, 24, 27, 30, 31, 34-36, 39, 42, 43, and 46-52 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,034,235 ("Sugiyama"), in view of Hammond et al., *Nature Genetics*, 2:110-119 (2001) ("Hammond"), and WO 03/061386 A1 ("Lopez"). Applicants traverse for the reasons described below.

Applicants understand the Examiner's argument as to the alleged obviousness of the rejected claims in this application to be as follows:

i. Sugiyama teaches SEQ ID NO:14 (exon 5 of WT1) and that antisense oligonucleotides can be made that comprise 5 to 50 continuous nucleotides or 5 to 70 nucleotides of sequences contained in any of the ten exons of WT1.

ii. Although Sugiyama does not teach an actual antisense oligonucleotide targeted to exon 5, Sugiyama does teach the use of antisense molecule targeted to exon 6.

iii. One of ordinary skill in the art could take the teachings in Sugiyama as they relate to exon 6 and apply them with a reasonable expectation of success to design and use an antisense molecule targeted to exon 5.

iv. Because Sugiyama does not teach an siRNA molecule, Hammond is relied on to teach that RNA interference is superior to antisense. Thus, according to the Examiner, Hammond would have motivated the ordinary artisan to make Applicants' claimed invention because Sugiyama "taught the desire to make antisense molecules targeted to SEQ ID NO:14 (exon 5)." Office Action at page 8.

v. One of ordinary skill in the art "would be able to reasonably expect success with a particular antisense molecule is predictive of success with siRNA that targets the same sequence targeted by the antisense molecule" in view of Vickers et al. which allegedly teaches "that one can make and use siRNAs comprising already known antisense oligonucleotide sequences." See, Office Action at pages 7-8.

The Office Action's reasoning makes several leaps of logic. *First*, it assumes that simply because one of Sugiyama's antisense molecules that is antisense to exon 6 of WT1 worked, an antisense molecule to a different, untested region - exon 5 - would also be effective in suppressing cell growth. *Second*, the Office Action assumes that the ordinary skilled artisan would choose the *particular* species of antisense molecules that target the *particular* region of exon 5 that is targeted by Applicants' siRNA molecule—again with no evidence whatsoever that this species *in particular* has any antisense activity. *Third*, despite the lack of disclosure in Sugiyama regarding any such antisense molecule's being prepared and tested to demonstrate activity, the Examiner alleges that one of ordinary skill in the art would convert this *hypothetical* antisense molecule targeting a *particular* region of exon 5 into an siRNA that suppresses cell growth, with a reasonable expectation of success. This allegation is surprising and entirely unjustified, given the fact that the ordinary artisan at the time of the filing of this application was fully aware of the unpredictability of individual siRNAs. For example, Davies et al., *Human Molecular Genetics*, 13:235-246 (2004) (document A8 in the Information Disclosure Statement filed January 18, 2008), state in the context of studies with siRNAs for WT1, "It has been documented that, while siRNA is generally highly effective in repressing gene expression in mammalian cells, **the effectiveness of any particular siRNA is difficult to predict**." (*see*, the carryover sentence of pages 236-237; emphasis supplied). In addition, McManus et al., *J. Immunol.*, 169:5754-5760 (2002) (document 1 in the Information Disclosure Statement filed on September 21, 2010) states, in relevant part, "we observed that the **majority of** the synthetic CD4 and CD8a **siRNAs were noneffective at silencing**. . . An examination of the nucleotide sequences did not reveal any obvious differences between the effective and ineffective siRNAs" (page 5747, left column, first full paragraph; emphasis supplied). McManus shows that only one out of five siRNAs targeting CD4 mRNA was capable of reducing expression of CD4. Both Davies and McManus establish the unpredictability associated with siRNAs. Based on this

unpredictability, and the fact that Sugiyama did not demonstrate success with even one antisense molecule targeting SEQ ID NO:14, the ordinary artisan at the time of the filing of the present application would not have had any reasonable expectation that a hypothetical siRNA version of Sugiyama's hypothetical antisense molecule targeting SEQ ID NO:14 would be able to suppress WT1 expression and suppress cell growth.

The Office Action dismisses Davies by saying:

> It should be noted that the mere fact that predicting the effectiveness of siRNAs is difficult does not whatsoever indicate that making or synthesizing or producing the claimed invention would have been unpredictable at the time of filing.

To be clear, Applicants are not arguing argue that "making or synthesizing or producing the claimed invention" would have been unpredictable at the time of filing. Rather, Applicants are arguing that the ordinary artisan at the time of the filing of the present application would have had no reason to select the particular region of exon 5 of WT1 targeted by Applicants' claimed siRNA and make an siRNA from a *hypothetical* antisense molecule when it was unpredictable whether either the antisense molecule or the siRNA would be effective; and furthermore, would have had no expectation of success in view of the art-recognized unpredictability with respect to siRNAs in general (as explained above).

The Office Action relies on Vickers et al.[1] for the proposition that "one can make and use siRNAs comprising already known antisense oligonucleotide sequences." But Vickers does not help the Examiner because, as the Examiner admits, Vickers' teaching is directed to "already known antisense oligonucleotide sequences." That is, Vickers starts with antisense molecules that have been shown to be active, and compares each of those active antisense molecules with siRNA molecules targeting the same region targeted by the antisense molecule. In contrast, the present rejection is based on a reference (Sugiyama) in which the only disclosed active antisense molecules target regions *other than* the region that is the focus of the present claims. Nowhere in Sugiyama is there any teaching of an *effective* antisense molecule targeted to exon 5 of WT1. Thus, regardless of Vicker's teachings (or those of any of the other cited references), there is simply no reason to use the combined references cited in this rejection to arrive at Applicants'

[1] Applicants note that Vickers et al. is not set forth in the statement of the rejection.

invention. This is plainly a case in which impermissible hindsight reconstruction of Applicants' invention was employed.

Next, Applicants address the following statement in the Office Action at page 11, second full paragraph, directed at the evidence of *teaching-away* discussed at pages 10-11 of the response filed November 21, 2011:

> It is noted that neither Yamagami et al. nor Murata et al. have been relied upon in the instant rejection. Therefore, arguments discussing these references appear to be misplaced and will not be considered, addressed, or discussed by the Examiner.

Applicants respectfully submit that the Examiner committed clear legal error in not considering and addressing the teaching away in Yamagami et al. and Murata et al. simply because these references were not relied upon in the instant rejection. Applicants first draw the Examiner's attention to MPEP § 2141.02(I), which makes clear that obviousness must be viewed in the context of the art as a whole. "Art as a whole" plainly does not mean the few references selected by the Examiner as supposedly supporting a rejection. In *KSR Int'l Co. v Teleflex, Inc.*, 550 U.S. 398 (2007), the Supreme Court reaffirmed the principle that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." From this guidance by the Supreme Court in *KSR*, it should be abundantly clear that when "the prior art" (which certainly means much more than merely the limited set of references relied upon in a rejection or by a defendant in a litigation) teaches away, that teaching away must be considered by the Examiner or the reviewing court. MPEP § 2145(D)(3) states that: "The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." That the Examiner committed clear legal error in disregarding the teaching away in Yamagami et al. and Murata et al. is further evidenced by the Federal Circuit's decision in *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1998), where the court stated, in relevant part:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.
>
> In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed

> invention. The Commissioner argues that since the PTO is no longer relying on Farmer or the Bacon and Farmer article, the applicant is creating a "straw man." It is indeed pertinent that these references teach against the present invention. Evidence that supports, rather than negates, patentability must be fairly considered. (citations omitted)

Similarly, in *In re Hedges*, 783 F.2d 1038, 1039, 1041 (Fed. Cir. 1986), the Federal Circuit considered evidence of *teaching away* found in three references that were not part of the cited rejection and, in finding that those references did indeed teach away, held that "the prior art as a whole must be considered." Thus, in the present case, the Examiner cannot simply set aside Applicants evidence of teaching away, but rather must give full consideration to Applicants' evidence and either accept it as persuasive or provide an adequate justification for disbelieving it. Applicants respectfully submit that when the above arguments are properly considered, this obviousness rejection should be withdrawn.

Finally, Applicants note that the combined teachings of Sugiyama, Hammond, and Lopez also fail to suggest the subject matter of the newly added claims: claims 53-60. Nowhere in any of these references, either alone or taken together, is there any suggestion of an isolated DNA consisting of the *specific* sequence set forth in SEQ ID NO: 3 and optionally one or more transcription control sequences operably linked to the sequence of SEQ ID NO:3; or an isolated RNA consisting of an RNA sequence that is the RNA equivalent of the *specific* sequence set forth in SEQ ID NO:3 with/without one to eight overhanging nucleotides at either or both of the 5' and 3' termini of the RNA sequence; or a vector that expresses such RNA molecules. As shown in Example 1 of the application as filed, the sequence set forth in SEQ ID NO: 3 has the following structure: 5'- C CCT TCT GTC CAT TTC ACT GAG CTG GAG CT (DNA encoding a 30-mer antisense strand of the target RNA)-AAA ACT CGA GAA AA (loop sequence containing an XhoI site) -AG CTC CAG CTC AGT GAA ATG GAC AGA AGG G (DNA encoding a 30-mer sense strand of the target RNA)-GGTACCCCCGGATATCTTTTTTT-3'. In contrast, the sequence set forth in SEQ ID NO: 14 of Sugiyama is: 5' AGTTGCTGCT GGGAGCTCCA GCTCAGTGAA ATGGACAGAA GGGCAGAGCA A 3'. The sequence set forth in SEQ ID NO:3 is clearly different from the sequence set forth in SEQ ID NO:14 of Sugiyama. When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention – including all its limitations – with the teachings of the

prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Int'l. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). The combined teachings of Sugiyama, Hammond, and Lopez simply fail to suggest the subject matter of the new claims.

For at least the foregoing reasons, Applicants assert that these references, taken alone or in combination, do not establish a *prima facie* case of obviousness. Accordingly, Applicants request that the Examiner reconsider and withdraw the rejection.

CONCLUSION

Applicants submit that all pending claims are in condition for allowance and thus request the timely issuance of a Notice of Allowability. If a discussion would be helpful to expedite prosecution, the Examiner is invited to call the undersigned at the telephone number provided below.

Applicants petition for a one-month extension of time to respond to the Office Action. Please apply any necessary charges or credits to Deposit Account No. 06-1050, referencing the above attorney docket number.

Respectfully submitted,

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